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(54) Title: N–TERMINALLY MODIFIED GLP–1 DERIVATIVES

(57) Abstract

The present invention relates to N–terminally modified derivatives of human glucagon–like peptide–1 (GLP–1) and analogues thereof having a protracted profile of action, as well as the use of such derivatives in pharmaceutical compositions for the treatment of obesity, insulin dependent or non–insulin dependent diabetes mellitus. The GLP–1 derivatives have a lipophilic substituent attached to at least one amino acid residue and are substituted at the N–terminal end with a substituent comprising an optionally substituted 5– or 6–membered ring system, e.g. an imidazole.

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N-TERMINALLY MODIFIED GLP-1 DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments and analogues thereof having a protracted profile of action and to the use of such derivatives in pharmaceutical compositions.

BACKGROUND OF THE INVENTION

GLP-1 (Glucacon-Like-Peptide-1) is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism. Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised *i.a.* in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1(7-36)amide, GLP-1(7-37) and GLP-2 occurs mainly in the L-cells.

WO 87/06941 (The General Hospital Corporation) disclose peptide fragments which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulinotropic agent.

WO 90/11296 (The General Hospital Corporation) disclose peptide fragments which comprise GLP-1(7-36) and functional derivatives thereof and have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1(1-36) or GLP-1(1-37) and to their use as insulinotropic agents.

The amino acid sequence of GLP-1(7-36)amide and GLP-1(7-37) is:

```
 7   8   9  10  11  12  13  14  15  16  17  18  19  20  21  22  23
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-

 24  25  26  27  28  29  30  31  32  33  34  35  36                (I)
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X
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wherein X is NH_2 for GLP-1(7-36)amide and X is Gly-OH for GLP-1(7-37).

WO 91/11457 (Buckley *et al.*) discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37.

WO 98/08871 discloses GLP-1 derivatives in which a lipophilic substituent is attached to at least one amino acid residue. The lipophilic substituents are in particular long-chain groups containing e.g. 12-24 carbon atoms.

EP 0708179-A2 (Eli Lilly & Co.) discloses GLP-1 analogues and derivatives that include an N-terminal imidazole group and optionally an unbranched C_8-C_{10} acyl group in attached to the lysine residue in position 34.

It is an object of the present invention to provide improved GLP-1 derivatives.

SUMMARY OF THE INVENTION

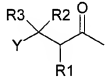
In its broadest aspect, the present invention relates to derivatives of GLP-1(7-B) and analogues thereof. The derivatives according to the invention have interesting pharmacological properties, including a protracted profile of action. The derivatives also are more metabolically and physically stable, and more soluble.

The GLP-1 derivatives and analogues of the present invention comprise a lipophilic substituent (optionally via a spacer) attached to at least one amino acid residue and the N-terminal amino acid, i.e., the histidine residue at position 7 is modified. The lipophilic substituent is in particular a long-chain group of the type described in WO 98/08871 (Novo Nordisk A/S), and the N-terminal substituent comprises an optionally substituted 5- or 6-membered ring system, e.g. an imidazole.

Accordingly, the invention relates to a GLP-1 derivative comprising a parent peptide of formula II

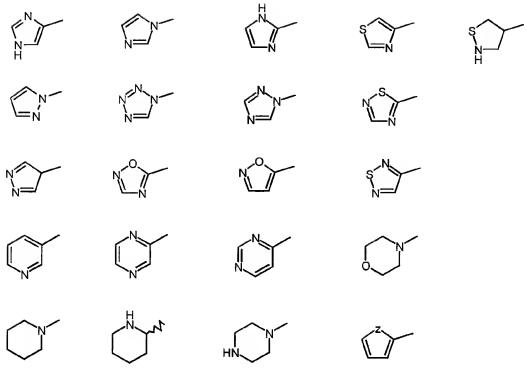
A–HN-GLP-1(8-B)-X (II)

wherein

A is:  or  or 

wherein R^1, R^2 and R^3 are independently H, lower alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy having 1 to 6 carbon atoms, halogen, SO_2-(lower alkyl) or CF_3, said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl or lower alkoxy having 1-6 carbon atoms, halogen, SO_2-(lower alkyl), NH-CO-(lower alkyl) or CF_3, or R^1 and R^2 may together form a bond;

Y is a five or six membered ring system selected from the group consisting of:



wherein Z is N, O or S, said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH_2, NO_2, OH, lower alkyl, lower alkoxy, halogen, CF_3 and aryl;

B is an integer in the range of 35-45; and

X is –OH, $–NH_2$, or a C_{1-6} alkyl amide or C_{1-6} dialkyl amide group;

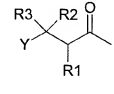
or an analogue thereof;

said GLP-1 derivative or analogue comprising a lipophilic substituent attached to at least one amino acid residue thereof.

In particular, the invention relates to GLP-1 derivatives of formula II

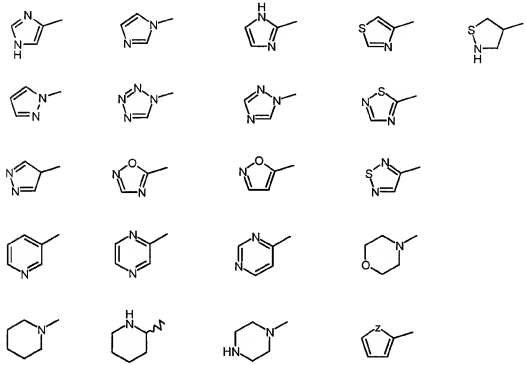
A–HN-GLP-1(8-B)-X (II)

wherein

A is:  or  or 

wherein R^1, R^2 and R^3 are independently H, lower alkyl, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy, halogen, SO_2-(lower alkyl) or CF_3, wherein said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl or lower alkoxy

having 1-6 carbon atoms, halogen, SO_2-(lower alkyl), NH-CO-(lower alkyl) or CF_3, or R^1 and R^2 may together form a bond; and Y is a five or six membered ring system selected from the group consisting of:



wherein Z is N, O or S, and said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH_2, NO_2, OH, lower alkyl, lower alkoxy, halogen, CF_3 and aryl (i.e., optionally substituted phenyl, as define above), provided that A is not histidine;

B is an integer in the range of 35-45; and

X is –OH, $–NH_2$, or a C_{1-6} alkyl amide or C_{1-6} dialkyl amide group;

or an analogue thereof;

wherein a lipophilic substituent (optionally via a spacer) is attached to at least one amino acid residue provided that when the lipophilic substituent is an acyl group and no spacer is present, then the acyl group contains at least 12 carbon atoms.

DETAILED DESCRIPTION OF THE INVENTION

A simple system is used to describe the GLP-1 derivatives of the present invention. For example, Gly^8-GLP-1(7-37) designates a peptide which relates to GLP-1(1-37) by the deletion of the amino acid residues at positions 1 to 6 and the substitution of the naturally occurring amino acid residue in position 8 (Ala) with Gly. Similarly, $Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37)

designates GLP-1(7-37) wherein the ε-amino group of the Lys residue in position 34 has been tetradecanoylated. Where a reference is made to C-terminally extended GLP-1 analogues, the amino acid residue in position 38 is Arg unless otherwise indicated, the amino acid residue in position 39 is also Arg unless otherwise indicated and the amino acid residue in position 40 is Asp unless otherwise indicated. Also, if a C-terminally extended analogue extends to position 41, 42, 43, 44 or 45, the amino acid sequence of this extension is as in the corresponding sequence in human preproglucagon unless otherwise indicated.

The present invention relates to derivatives of native GLP-1 and derivatives of GLP-1 analogs. In a preferred embodiment, the derivatives are derivatives of GLP-1(7-45) or a fragment thereof. In a more preferred embodiment, the derivatives are derivatives of native GLP-1(7-36). In another more preferred embodiment, the derivatives are derivatives of native GLP-1(7-37). In another more preferred embodiment, the derivatives are derivatives of native GLP-1(7-38).

GLP-1 Analogs

The present invention also relates to derivatives of analogs of GLP-1. The term "analogue" is defined herein as a peptide which relates to a parent peptide by the substitution of one or more amino acid residues of the parent peptide with other amino acid residue(s).

In the GLP-1 derivatives of formula II, B is preferably 36, 37 or 38.

In the GLP-1 derivatives of formula II, up to fifteen, preferably up to ten amino acid residues may be exchanged with any α-amino acid residue, in particular with any α-amino acid residue which can be coded for by the genetic code. Preferred analogues are those in which up to six amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code.

Preferred GLP-1 derivatives or analogues are those in which:

B is 36, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34} and Lys^{36};

B is 37, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34}, Lys^{36} and Lys^{37}; or

B is 38, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34}, Lys^{36} and Lys^{38}.

In a further preferred embodiment, a parent peptide for a derivative of the invention is Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{40}$-GLP-1(7-40);

$Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37);
$Arg^{26}Lys^{39}$-GLP-1(7-39); $Arg^{34}Lys^{40}$-GLP-1(7-40);
$Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40);
$Gly^{8}Arg^{26}$-GLP-1(7-37); $Gly^{8}Arg^{34}$-GLP-1(7-37);
$Gly^{8}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37);
$Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{40}$-GLP-1(7-40);
$Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37);
$Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40);
$Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); or
$Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

In a further preferred embodiment, a parent peptide for a derivative of the invention is:
$Arg^{26,34}Lys^{38}$GLP-1(7-38);
$Arg^{26,34}Lys^{39}$GLP-1(7-39);
$Arg^{26,34}Lys^{40}$GLP-1(7-40);
$Arg^{26,34}Lys^{41}$GLP-1(7-41);
$Arg^{28,34}Lys^{42}$GLP-1(7-42);
$Arg^{26,34}Lys^{43}$GLP-1(7-43);
$Arg^{26,34}Lys^{44}$GLP-1(7-44);
$Arg^{28,34}Lys^{45}$GLP-1(7-45);
$Arg^{26}Lys^{38}$GLP-1(7-38);
$Arg^{34}Lys^{38}$GLP-1(7-38);
$Arg^{28,34}Lys^{36,38}$GLP-1(7-38);
$Arg^{26,34}Lys^{38}$GLP-1(7-38);
$Arg^{26}Lys^{39}$GLP-1(7-39);
$Arg^{34}Lys^{39}$GLP-1(7-39); or
$Arg^{26,34}Lys^{36,39}$GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising Arg^{26}-GLP-1(7-37), Arg^{34}-GLP-1(7-37), Lys^{36}-GLP-1(7-37), $Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Arg^{26}Lys^{36}$-GLP-1(7-37), $Arg^{34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}$-GLP-1(7-37), $Gly^{8}Arg^{34}$-GLP-1(7-37), $Gly^{8}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37) and $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{26}Lys^{38}$-GLP-1(7-38), $Arg^{26,34}Lys^{38}$-GLP-1(7-38), $Arg^{26,34}Lys^{36,38}$-GLP-1(7-38), $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-38) and $Gly^{8}Arg^{26,34}Lys^{36,38}$-GLP-1(7-38).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{26}Lys^{39}$-GLP-1(7-39), $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39), $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39) and $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{34}Lys^{40}$-GLP-1(7-40), $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40), $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40) and $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

Arg^{26}-GLP-1(7-36); Arg^{34}-GLP-1(7-36); $Arg^{26,34}Lys^{36}$-GLP-1(7-36); Arg^{26}-GLP-1(7-36)amide; Arg^{34}-GLP-1(7-36)amide; $Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); Arg^{26}-GLP-1(7-38); Arg^{34}-GLP-1(7-38); $Arg^{26,34}Lys^{38}$GLP-1(7-38); Arg^{28}-GLP-1(7-39); Arg^{34}-GLP-1(7-39); $Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26}$-GLP-1(7-36); $Gly^{8}Arg^{34}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{26}$-GLP-1(7-36)amide; $Gly^{8}Arg^{34}$-GLP-1(7-36)amide; $Gly^{8}Arg^{26,34}Lys^{38}$-GLP-1(7-36)amide; $Gly^{8}Arg^{26}$-GLP-1(7-37); $Gly^{8}Arg^{34}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}$-GLP-1(7-38); $Gly^{8}Arg^{34}$-GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Arg^{26}$-GLP-1(7-39); $Gly^{8}Arg^{34}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{26}$-GLP-1(7-36); $Val^{8}Arg^{34}$-GLP-1(7-36); $Val^{8}Arg^{28,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{26}$-GLP-1(7-36)amide; $Val^{8}Arg^{34}$-GLP-1(7-36)amide; $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Arg^{26}$-GLP-1(7-37); $Val^{8}Arg^{34}$-GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26}$-GLP-1(7-38); $Val^{8}Arg^{34}$-GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Arg^{26}$-GLP-1(7-39); $Val^{8}Arg^{34}$-GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Arg^{26}$-GLP-1(7-36); $Ser^{8}Arg^{34}$-GLP-1(7-36); $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Arg^{26}$-GLP-1(7-36)amide; $Ser^{8}Arg^{34}$-GLP-1(7-36)amide; $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Arg^{26}$-GLP-1(7-37); $Ser^{8}Arg^{34}$-GLP-1(7-37); $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Ser^{8}Arg^{26}$-GLP-1(7-38); $Ser^{8}Arg^{34}$-GLP-1(7-38); $Ser^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Arg^{26}$-GLP-1(7-39); $Ser^{8}Arg^{34}$-GLP-1(7-39); $Ser^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Thr^{8}Arg^{26}$-GLP-1(7-36); $Thr^{8}Arg^{34}$-GLP-1(7-36);
$Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Arg^{26}$-GLP-1(7-36)amide;
$Thr^{8}Arg^{34}$-GLP-1(7-36)amide; $Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide;
$Thr^{8}Arg^{26}$-GLP-1(7-37); $Thr^{8}Arg^{34}$-GLP-1(7-37);
$Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Thr^{8}Arg^{26}$-GLP-1(7-38);
$Thr^{8}Arg^{34}$-GLP-1(7-38); $Thr^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38);
$Thr^{8}Arg^{26}$-GLP-1(7-39); $Thr^{8}Arg^{34}$-GLP-1(7-39);
$Thr^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36);
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$Val^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Glu^{38}Arg^{28,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36);
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$Val^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Val^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide;
$Ser^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Ser^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Ser^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Ser^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Ser^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Thr^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Thr^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39);
$Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide;
$Thr^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);
$Thr^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37);

Thr^{8}Asp^{37}Arg^{26,34}Lys^{38}GLP-1(7-38); Thr^{8}Asp^{38}Arg^{26,34}Lys^{39}-GLP-1(7-39); Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36); Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36)amide; Gly^{8}Glu^{35}Arg^{26,34}Lys^{37}GLP-1(7-37); Gly^{8}Glu^{37}Arg^{26,34}Lys^{38}GLP-1(7-38); Gly^{8}Glu^{38}Arg^{26,34}Lys^{39}-GLP-1(7-39); Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36); Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36)amide; Gly^{8}Glu^{36}Arg^{26,34}Lys^{37}GLP-1(7-37); Gly^{8}Glu^{37}Arg^{26,34}Lys^{38}GLP-1(7-38); Gly^{8}Glu^{38}Arg^{26,34}Lys^{39}-GLP-1(7-39); Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36); Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36)amide; Gly^{8}Asp^{36}Arg^{26,34}Lys^{37}GLP-1(7-37); Gly^{8}Asp^{37}Arg^{26,34}Lys^{38}GLP-1(7-38); Gly^{8}Asp^{38}Arg^{26,34}Lys^{39}-GLP-1(7-39); Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36); Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}-GLP-1(7-36)amide; Gly^{8}Asp^{36}Arg^{26,34}Lys^{37}GLP-1(7-37); Gly^{8}Asp^{37}Arg^{26,34}Lys^{38}GLP-1(7-38); Gly^{8}Asp^{38}Arg^{26,34}Lys^{39}-GLP-1(7-39); Arg^{26,34}Lys^{18}-GLP-1(7-36); Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Arg^{26,34}Lys^{18}GLP-1(7-37); Arg^{26,34}Lys^{18}GLP-1(7-38); Gly^{8}Asp^{18}Arg^{26,34}Lys^{18}-GLP-1(7-36); Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}-GLP-1(7-36); Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}GLP-1(7-37); Gly^{8}Asp^{18}Arg^{26,34}Lys^{18}GLP-1(7-38); Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}GLP-1(7-38); Arg^{26,34}Lys^{23}-GLP-1(7-36); Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Arg^{26,34}Lys^{23}GLP-1(7-37); Arg^{26,34}Lys^{23}GLP-1(7-38); Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}-GLP-1(7-36); Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}-GLP-1(7-36); Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}GLP-1(7-37); Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}GLP-1(7-38); Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}GLP-1(7-38); Arg^{26,34}Lys^{27}-GLP-1(7-36); Arg^{26,34}Lys^{27}-GLP-1(7-36)amide; Arg^{26,34}Lys^{27}GLP-1(7-37); Arg^{26,34}Lys^{27}GLP-1(7-38); Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}-GLP-1(7-36); Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}-GLP-1(7-36); Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}-GLP-1(7-36)amide; Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}-GLP-1(7-36)amide; Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}GLP-1(7-37); Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}GLP-1(7-38); Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}GLP-1(7-38); Arg^{26,34}Lys^{18}-GLP-1(7-36); Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Arg^{26,34}Lys^{18}GLP-1(7-37); Arg^{26,34}Lys^{18}GLP-1(7-38); Val^{8}Asp^{19}Arg^{26,34}Lys^{18}-GLP-1(7-36); Val^{8}Asp^{17}Arg^{26,34}Lys^{18}-GLP-1(7-36); Val^{8}Asp^{19}Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Val^{8}Asp^{17}Arg^{26,34}Lys^{18}-GLP-1(7-36)amide; Val^{8}Asp^{19}Arg^{26,34}Lys^{18}GLP-1(7-37); Val^{8}Asp^{19}Arg^{26,34}Lys^{18}GLP-1(7-38); Val^{8}Asp^{17}Arg^{26,34}Lys^{18}GLP-1(7-38); Arg^{26,34}Lys^{23}-GLP-1(7-36); Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Arg^{26,34}Lys^{23}GLP-1(7-37); Arg^{26,34}Lys^{23}GLP-1(7-38); Val^{8}Asp^{24}Arg^{26,34}Lys^{23}-GLP-1(7-36); Val^{8}Asp^{22}Arg^{26,34}Lys^{23}-GLP-1(7-36); Val^{8}Asp^{24}Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Val^{8}Asp^{22}Arg^{26,34}Lys^{23}-GLP-1(7-36)amide; Val^{8}Asp^{24}Arg^{26,34}Lys^{23}GLP-1(7-37); Val^{8}Asp^{24}Arg^{26,34}Lys^{23}GLP-1(7-38); Val^{8}Asp^{22}Arg^{26,34}Lys^{23}GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38);

$Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38);

$Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38);

$Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Thr^{8}Asp^{19}Arg^{28,34}Lys^{18}$-GLP-1(7-36); $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Thr^{8}Asp^{19}Arg^{28,34}Lys^{18}$-GLP-1(7-36)amide; $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Thr^{8}Asp^{19}Arg^{28,34}Lys^{18}$GLP-1(7-37); $Thr^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38);

$Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); or

$Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

$Arg^{26}Lys^{36}$-GLP-1(7-36); $Arg^{34}Lys^{36}$-GLP-1(7-36); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); $Arg^{26}Lys^{37}$-GLP-1(7-37); $Arg^{34}Lys^{37}$-GLP-1(7-37); $Arg^{26}Lys^{39}$-GLP-1(7-39); $Arg^{34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39);

$Arg^{26}Lys^{18}$-GLP-1(7-36); $Arg^{34}Lys^{18}$-GLP-1(7-36); $Arg^{26}Lys^{18}$GLP-1(7-37); $Arg^{34}Lys^{18}$GLP-1(7-37); $Arg^{26}Lys^{18}$GLP-1(7-38); $Arg^{34}Lys^{18}$GLP-1(7-38); $Arg^{26}Lys^{18}$GLP-1(7-39); $Arg^{34}Lys^{18}$GLP-1(7-39); $Arg^{26}Lys^{23}$-GLP-1(7-36); $Arg^{34}Lys^{23}$-GLP-1(7-36); $Arg^{26}Lys^{23}$GLP-1(7-37); $Arg^{34}Lys^{23}$GLP-1(7-37); $Arg^{26}Lys^{23}$GLP-1(7-38); $Arg^{34}Lys^{23}$GLP-1(7-38); $Arg^{26}Lys^{23}$GLP-1(7-39); $Arg^{34}Lys^{23}$GLP-1(7-39); $Arg^{26}Lys^{27}$-GLP-1(7-36); $Arg^{34}Lys^{27}$-GLP-1(7-36); $Arg^{26}Lys^{27}$GLP-1(7-37); $Arg^{34}Lys^{27}$GLP-1(7-37); $Arg^{26}Lys^{27}$GLP-1(7-38); $Arg^{34}Lys^{27}$GLP-1(7-38); $Arg^{26}Lys^{27}$GLP-1(7-39); $Arg^{34}Lys^{27}$GLP-1(7-39); $Arg^{26,34}Lys^{18,38}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Arg^{26,34}Lys^{27,38}$GLP-1(7-38); $Arg^{26,34}Lys^{27,39}$GLP-1(7-39); Gly^{8}GLP-1(7-36); Gly^{8}GLP-1(7-37); Gly^{8}GLP-1(7-38); Gly^{8}GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{37}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{37}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Gly^{8}Arg^{26}Lys^{18}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{18}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-39); $Gly^{8}Arg^{26}Lys^{23}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{23}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-39); $Gly^{8}Arg^{26}Lys^{27}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{27}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{18,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{27,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{27,39}$GLP-1(7-39); Val^{8}GLP-1(7-36); Val^{8}GLP-1(7-37); Val^{8}GLP-1(7-38); Val^{8}GLP-1(7-39)

$Val^{8}Arg^{26}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26}Lys^{37}$-GLP-1(7-37); $Val^{8}Arg^{34}Lys^{37}$-GLP-1(7-37); $Val^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{34}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Val^{8}Arg^{26}Lys^{18}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{18}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{18}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{18}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{19}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{19}$GLP-1(7-39); $Val^{8}Arg^{26}Lys^{23}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{23}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-39); $Val^{8}Arg^{26}Lys^{27}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{27}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{18,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{27,38}$GLP-1(7-38); or $Val^{8}Arg^{26,34}Lys^{27,38}$GLP-1(7-39).

In a most preferred embodiment, the present invention relates to derivatives of GLP-1 analogues of formula III:

```
      7   8   9  10  11  12  13  14  15  16  17
Xaa-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

      18  19  20  21  22  23  24  25  26  27  28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-

      29  30  31  32  33  34  35  36  37  38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

      39  40  41  42  43  44  45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa
```

(III)

wherein

Xaa at position 7 is any of the groups A (as defined herein),

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 9 is Glu, Asp, or Lys,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,
Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,
Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 21 is Glu, Asp, or Lys,
Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,
Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,
Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,
Xaa at position 27 is Glu, Asp, or Lys,
Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,
Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,
Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Met, Leu, Ile, Glu, Asp, or Lys,
Xaa at position 34 is Lys, Arg, Glu, Asp, or His,
Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 36 is Arg, Lys, Glu, Asp, or His,
Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,
Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,
Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,
Xaa at position 40 is Asp, Glu, or Lys, or is deleted,
Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,
Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,
Xaa at position 43 is Glu, Asp, or Lys, or is deleted,
Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and
Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C-1-6-ester thereof, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

wherein

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted,

(ii) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(iii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five or six.

The total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 does not exceed six. Preferably, the number of different amino acids is five. More preferably, the number of different amino acids is four. Even more preferably, the number of different amino acids is three. Even more preferably, the number of different amino acids is two. Most preferably, the number of different amino acids is one. In order to determine the number of different amino acids, one should compare the amino acid sequence of the derivative of the GLP-1 analog of the present invention with the corresponding native GLP-1. For example, there are two different amino acids (at positions 8 and 26) between the derivative $Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40) and the corresponding native GLP-1 (i.e., GLP-1(7-40)). Similarly, there is only one different amino acid (at position 34) between the derivative $Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))Arg^{34}-GLP-1(7-40) and the corresponding native GLP-1.

The derivatives of the GLP-1 analogs of the present invention preferably have only one or two Lys. The ε-amino group of one or both Lys is substituted with a lipophilic substituent, Preferably, the derivatives of the GLP-1 analogs of the present invention have only one Lys. In a more preferred embodiment, there is only one Lys which is located at the carboxy terminus of the derivative of the GLP-1 analogs. In an even more preferred embodiment, the derivatives of the GLP-1 analogs of the present invention have only one Lys and Glu or Asp is adjacent to Lys.

In a preferred embodiment, the amino acids at positions 37-45 are absent.

In another preferred embodiment, the amino acids at positions 38-45 are absent.

In another preferred embodiment, the amino acids at positions 39-45 are absent.

In another preferred embodiment, Xaa at position 8 is Ala, Gly, Ser, Thr, or Val.

In another preferred embodiment, Xaa at position 9 is Glu.

In another preferred embodiment, Xaa at position 11 is Thr.

In another preferred embodiment, Xaa at position 14 is Ser.

In another preferred embodiment, Xaa at position 16 is Val.

In another preferred embodiment, Xaa at position 17 is Ser.

In another preferred embodiment, Xaa at position 18 is Ser, Lys, Glu, or Asp.

In another preferred embodiment, Xaa at position 19 is Tyr, Lys, Glu, or Asp.

In another preferred embodiment, Xaa at position 20 is Leu, Lys, Glu, or Asp.

In another preferred embodiment, Xaa at position 21 is Glu, Lys, or Asp.

In another preferred embodiment, Xaa at position 22 is Gly, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 23 is Gln, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 24 is Ala, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 25 is Ala, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 26 is Lys, Glu, Asp, or Arg.

In another preferred embodiment, Xaa at position 27 is Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 30 is Ala, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 31 is Trp, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 32 is Leu, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 33 is Val, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 34 is Lys, Arg, Glu, or Asp.

In another preferred embodiment, Xaa at position 35 is Gly, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 36 is Arg, Lys, Glu, or Asp.

In another preferred embodiment, Xaa at position 37 is Gly, Glu, Asp, or Lys.

In another preferred embodiment, Xaa at position 38 is Arg, or Lys, or is deleted.

In another preferred embodiment, Xaa at position 39 is deleted.

In another preferred embodiment, Xaa at position 40 is deleted.

In another preferred embodiment, Xaa at position 41 is deleted.

In another preferred embodiment, Xaa at position 42 is deleted.

In another preferred embodiment, Xaa at position 43 is deleted.

In another preferred embodiment, Xaa at position 44 is deleted.

In another preferred embodiment, Xaa at position 45 is deleted.

In another preferred embodiment, Xaa at position 26 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at position 26 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at position 26 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at position 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at position 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at positions 26 and 34 is Arg, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

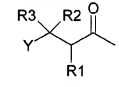
In another preferred embodiment, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

Derivatives

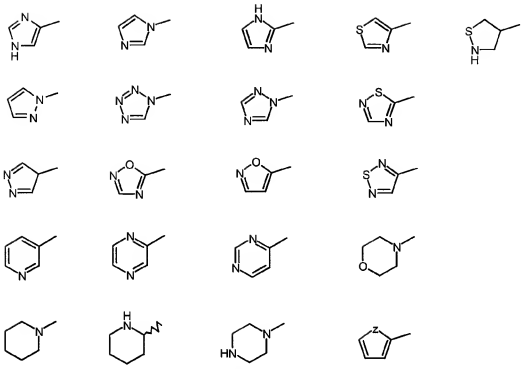
The term "derivative" is defined as a modification of one or more amino acid residues of a peptide by chemical means, either with or without an enzyme, *e.g.* by alkylation, acylation, ester formation or amide formation.

Modified Histidine

In the GLP-1 derivatives of the present invention, the histidine residue at position 7 is modified. Specifically the histidine residue at position 7 is replaced with a group A wherein

A is:  or  or 

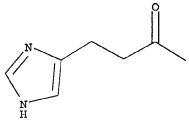
wherein R^1, R^2 and R^3 are independently H, lower alkyl, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy, halogen, SO_2-(lower alkyl) or CF_3, wherein said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl, lower alkoxy, halogen, SO_2-(lower alkyl), NH-CO-(lower alkyl) or CF_3, or R^1 and R^2 may together form a bond; and Y is a five or six membered ring system selected from the group consisting of:



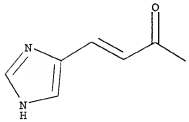
wherein Z is N, O or S, and said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH_2, NO_2, OH, lower alkyl, lower alkoxy, halogen, CF_3 and aryl (i.e. optionally substituted phenyl as defined above), provided that A is not histidine.

The terms "lower alkyl" and "lower alkoxy" refer to an alkyl or alkoxy group, respectively, having 1-6 carbon atoms.

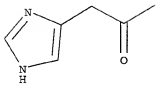
In a preferred embodiment, A is:



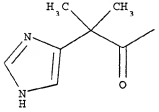
In another preferred embodiment, A is:



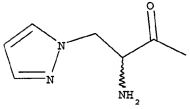
In another preferred embodiment, A is:



In another preferred embodiment, A is:



In another preferred embodiment, A is:



In another preferred embodiment, A is 4-imidazopropionyl.

In another preferred embodiment, A is 4-imidazoacetyl.

In another preferred embodiment, A is 4-imidazo-α,α-dimethyl-acetyl.

In another preferred embodiment the GLP-1 derivatives of formula II is selected from desamino-His^{7},Arg^{26},Lys^{34} (N$^{\varepsilon}$-(γ-glutamyl(N$^{\alpha}$-hexadecanoyl))) GLP-1 (7-37)-OH, desamino-His^{7},Arg^{26},Lys^{34} (N$^{\varepsilon}$-(γ-glutamyl(N$^{\alpha}$-octanoyl))) GLP-1 (7-37)-OH, desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-glutamyl(N$^{\alpha}$-hexadecanoyl))) GLP-1 (7-37), desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\gamma}$-hexadecanoyl))) GLP-1 (7-37), desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(β-alanyl(N$^{\gamma}$-hexadecanoyl))) GLP-1 (7-37), Arg^{34},Ala^{8}(N$^{\alpha}$-(imidazol-4-ylprop-2-enoyl),Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\gamma}$-hexadecanoyl))) GLP-1 (8-37), Arg^{34},Ala^{8}(N$^{\alpha}$-(imidazol-4-ylacetyl),Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\gamma}$-hexadecanoyl))) GLP-1 (8-37), desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\gamma}$-tetradecanoyl))) GLP-1 (7-37), desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\gamma}$-octadecanoyl))) GLP-1 (7-37).

Lipophilic Substituents

To obtain a satisfactory protracted profile of action of the GLP-1 derivative, the lipophilic substituents attached to the parent GLP-1 peptide preferably comprises 4-40 carbon atoms, more preferably 8-25 carbon atoms, in particular from 12-24 carbon atoms and most preferably

12-18 carbon atoms. A lipophilic substituent may be attached to an amino group of the parent GLP-1 peptide by means of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid residue to which it is attached.

In a preferred embodiment, the GLP-1 derivatives of the present invention have three lipophilic substituents.

In a more preferred embodiment, the GLP-1 derivatives of the present invention have two lipophilic substituents.

In an even more preferred embodiment, the GLP-1 derivatives of the present invention have one lipophilic substituent.

Each lipophilic substituent can be attached to (a) the free amino group of the N-terminal amino acid, (b) the free carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys and/or (d) the carboxy group which is part of the R group of Asp or Glu.

In a preferred embodiment, a lipophilic substituent is attached to only the carboxy group which is part of the R group of Asp or Glu.

In a preferred embodiment, a lipophilic substituent is attached to only the free carboxy group of the C-terminal amino acid.

In another preferred embodiment, a lipophilic substituent is attached to only an ε-amino group of Lys.

In one preferred embodiment of the invention, the lipophilic substituent is attached to the parent GLP-1 peptide by means of a spacer in such a way that a carboxyl group of the spacer forms an amide bond with an amino group of the parent GLP-1 peptide. In a preferred embodiment, the spacer is an α,ω-amino acid. Examples of suitable spacers are succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys. When the spacer is succinic acid, one carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the other carboxyl group thereof may form an amide bond with an amino group of the lipophilic substituent. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one preferred embodiment, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another preferred embodiment such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent. Other preferred spacers are γ-L-glutamyl, β-L-asparagyl, glycyl, β-L-alanyl, and α-(γ-aminobutanoyl).

In another preferred embodiment of the present invention, the lipophilic substituent has a group which can be negatively charged. One preferred group which can be negatively charged is a carboxylic acid group.

In a further preferred embodiment, the lipophilic substituent comprises from 6 to 40 carbon atoms, more preferably from 12 to 25 carbon atoms, and most preferably 12 to 18 carbon atoms.

In a further preferred embodiment, the lipophilic substituent is attached to the parent peptide by means of a spacer which is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent.

In a further preferred embodiment, the lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. In the present text, the phrase "a dipeptide such as Gly-Lys" means a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and wherein the N-terminal amino acid residue is selected from the group comprising Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe and Pro.

In a further preferred embodiment, the lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys or Met, or is a dipeptide such as Gly-Lys and wherein an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further preferred embodiment, the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In a further preferred embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In a further preferred embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid.

In a further preferred embodiment, the lipophilic substituent is an acyl group selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group comprising $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-. In a most preferred embodiment, the lipophilic substituent is tetradecanoyl. In another most preferred embodiment, the lipophilic substituent is hexadecanoyl.

In a further preferred embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

In a further preferred embodiment, the lipophilic substituent is an acyl group selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group comprising $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH$-$CO(CH_2)_2CO$-, wherein p is an integer of from 8 to 33, preferably from 12 to 28.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO$-$NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO$-$NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

In a further preferred embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from 8 to 24.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula -$NHCH(COOH)(CH_2)_4NH$-$CO(CH_2)_uCH_3$, wherein u is an integer of from 8 to 18.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO$-NH-$(CH_2)_z$-CO, wherein n is an integer of from 8 to 24 and z is an integer of from 1 to 6.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula -$NHCH(COOH)(CH_2)_4NH$-$COCH((CH_2)_2COOH)NH$-$CO(CH_2)_wCH_3$, wherein w is an integer of from 10 to 16.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula -$NHCH(COOH)(CH_2)_4NH$-$CO(CH_2)_2CH(COOH)NH$-$CO(CH_2)_xCH_3$, wherein x is an integer of from 10 to 16.

In a further preferred embodiment, the lipophilic substituent with the attached spacer is a group of the formula -$NHCH(COOH)(CH_2)_4NH$-$CO(CH_2)_2CH(COOH)NHCO(CH_2)_yCH_3$, wherein y is zero or an integer of from 1 to 22.

In a further preferred embodiment, the lipophilic substituent can be negatively charged. Such a lipophilic substituent can for example be a substituent which has a carboxyl group.

Other Derivatives

The derivatives of GLP-1 analogues of the present invention may be in the form of one or more of (a) a C-1-6-ester, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide, and (c) a pharmaceutical salt. In a preferred embodiment, the derivatives of GLP-1 analogues are in the form of an acid addition salt or a carboxylate salt, most preferably in the form of an acid addition salt.

Pharmaceutical Compositions

The present invention also relates to pharmaceutical compositions comprising a derivative of a GLP-1 analog of the present invention and a pharmaceutically acceptable vehicle or carrier.

Preferably, the pharmaceutical compositions comprise an isotonic agent, a preservative and a buffer. Examples of isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol. Suitable buffers include sodium acetate, sodium citrate, glycylglycine, histidine, 2-phenylethanol and sodium phosphate.

The pharmaceutical compositions preferably further comprise a surfactant in order to improve the solubility and/or the stability of the GLP-1 derivative. Preferably, the surfactant is poloxymer 188, tween 20 or tween 80.

The pharmaceutical compositions preferably also comprise zinc.

The pharmaceutical compositions preferably also comprise protamine.

The pharmaceutial compositions preferably further comprise another antidiabetic agent. The term "antidiabetic agent" includes compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism.

In one embodiment of this invention, the antidiabetic agent is an insulin, more preferably human insulin.

In another embodiment the antidiabetic agent is a hypoglycaemic agent, preferably an oral hypoglycaemic agent. Oral hypoglycaemic agents are preferably selected from the group consisting of sulfonylureas, biguanides, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potasium channel openers, insulin sensitizers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism, compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the ß-cells. Preferred sulfonylureas are tolbutamide, glibenclamide, glipizide and gliclazide. A preferred biguanide is metformin. Preferred thiazolidinediones are troglitazone and ciglitazone. A

preferred glucosidase inhibitor is acarbose. Preferred agents acting on the ATP-dependent potassium channel of the ß-cells are: glibenclamide, glipizide, gliclazide, and repaglinide.

In a preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection. Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, *e.g.* a lyophilised product, which has to be dissolved in a solvent before it can be injected. The injectable solution preferably contains not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 derivative and, preferably, not more than about 100 mg/ml of the GLP-1 derivative.

The pharmaceutical compositions of the present invention also preferably comprise another anti-obesity drug.

In one embodiment of this invention, the antiobesity agent is leptin.

In another embodiment the antiobesity agent is amphetamin.

In another embodiment the antiobesity agent is dexfenfluramine.

In another embodiment the antiobesity agent is sibutramine.

In another embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is selected from a group of CART agonists, NPY antagonists, orexin antagonists, H3-antagonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, glucagon, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (Bromocriptin, Doprexin), lipase/amylase inhibitors, PPAR modulators, PXR modulators or TR β agonists.

A number of GLP-1 derivatives of the present invention exist in a partially structured micellar-like aggregated form when added to water or an aqueous solution. This structure makes them more soluble and stable in solution as compared to native GLP-1. The increased solubility and stability can be seen by comparing the solubility after 9 days of standing for a derivative and normal GLP-1(7-37) in a pharmaceutical formulation, e.g. 5 mM phosphate buffer, pH 6.9 added 0.1 M NaCl.

Circular Dichroism (CD) can be used to show that the GLP-1 derivatives have a certain partially structured conformation. In contrast to native GLP-1(7-37) the helix content of some GLP-1 derivatives of the present invention increases with increasing concentration, from 10-15% to 30-35% (at a concentration of 500 μM) in parallel with peptide self-association. For the GLP-1 derivatives forming partially structured micellar-like aggregates in aqueous solution the helix content remains constant above 30% at concentrations of 10 μM.

The size of the partially helical, micelle-like aggregates may be estimated by size-exclusion chromatography. Similarly, the apparent (critical micelle concentrations) CMC's of the peptides may be estimated from the concentration dependent fluorescence in the presence of appropriate dyes (e.g. Brito, R. & Vaz, W. (1986) Anal. Biochem. **152**, 250-255).

Thus, the present invention also relates to pharmaceutical compositions comprising water and a GLP-1 derivative of the present invention which has a helix content as measured by Circular Dichroism at 222 nm in H_2O at 22 ± 2°C exceeding 25%, preferably in the range of 25% to 50%, at a peptide concentration of about 10 μM.

Uses

The present invention also relates to the use of a GLP-1 derivative of the present invention for the preparation of a medicament which has a protracted profile of action relative to GLP-1(7-37).

The present invention also relates to the use of a GLP-1 derivative of the present invention for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

The present invention also relates to the use of a GLP-1 derivative of the present invention for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

The present invention also relates to the use of a GLP-1 derivative of the present invention to treat insulin resistance.

The present invention also relates to the use of a GLP-1 derivative of the present invention for the preparation of a medicament with protracted effect for the treatment of obesity.

The present invention relates to a method of treating insulin dependent or non-insulin dependent diabetes mellitus in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of the present invention together with a pharmaceutically acceptable carrier.

The present invention relates to a method of treating obesity in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of the present invention together with a pharmaceutically acceptable carrier.

The particular GLP-1 derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case.

The pharmaceutical compositions of the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the GLP-1 derivative in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 derivatives of the invention can also be administered transdermally, *e.g.* from a patch, optionally a iontophoretic patch, or transmucosally, *e.g.* bucally.

Methods of Production

The parent peptide can be produced by a method which comprises culturing a host cell containing a DNA sequence encoding the polypeptide and capable of expressing the polypeptide in a suitable nutrient medium under conditions permitting the expression of the peptide, after which the resulting peptide is recovered from the culture.

The medium used to culture the cells may be any conventional medium suitable for growing the host cells, such as minimal or complex media containing appropriate supplements. Suitable media are available from commercial suppliers or may be prepared according to published recipes (*e.g.* in catalogues of the American Type Culture Collection). The peptide produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, *e.g.* ammonium sulphate, purification by a variety of chromatographic procedures, *e.g.* ion exchange chromatography, gel filtration chromatography, affinity chromatography, or the like, dependent on the type of peptide in question.

The DNA sequence encoding the parent peptide may suitably be of genomic or cDNA origin, for instance obtained by preparing a genomic or cDNA library and screening for DNA sequences coding for all or part of the peptide by hybridisation using synthetic oligonucleotide probes in accordance with standard techniques (see, for example, Sambrook, J, Fritsch, EF and Maniatis, T, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, New York, 1989). The DNA sequence encoding the peptide may also be prepared synthetically by established standard methods, *e.g.* the phosphoamidite method described by Beaucage and Caruthers, *Tetrahedron Letters* **22** (1981), 1859 - 1869, or the method described by Matthes *et al.*, *EMBO Journal* **3** (1984), 801 - 805. The DNA sequence may also be prepared by polymerase chain reaction using specific primers, for instance as described in US 4,683,202 or Saiki *et al.*, *Science* **239** (1988), 487 - 491.

The DNA sequence may be inserted into any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, *i.e.* a vector which exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, *e.g.* a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

The vector is preferably an expression vector in which the DNA sequence encoding the peptide is operably linked to additional segments required for transcription of the DNA, such as a promoter. The promoter may be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA encoding the peptide of the invention in a variety of host cells are well known in the art, cf. for instance Sambrook *et al.*, *supra*.

The DNA sequence encoding the peptide may also, if necessary, be operably connected to a suitable terminator, polyadenylation signals, transcriptional enhancer sequences, and translational enhancer sequences. The recombinant vector of the invention may further comprise a DNA sequence enabling the vector to replicate in the host cell in question.

The vector may also comprise a selectable marker, *e.g.* a gene the product of which complements a defect in the host cell or one which confers resistance to a drug, *e.g.* ampicillin, kanamycin, tetracyclin, chloramphenicol, neomycin, hygromycin or methotrexate.

To direct a parent peptide of the present invention into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) may be provided in the recombinant vector. The secretory signal sequence is joined to the DNA sequence encoding the peptide in the correct reading frame. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the peptide. The secretory signal sequence may be that normally associated with the peptide or may be from a gene encoding another secreted protein.

The procedures used to ligate the DNA sequences coding for the present peptide, the promoter and optionally the terminator and/or secretory signal sequence, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook *et al.*, *supra*).

The host cell into which the DNA sequence or the recombinant vector is introduced may be any cell which is capable of producing the present peptide and includes bacteria, yeast, fungi

and higher eukaryotic cells. Examples of suitable host cells well known and used in the art are, without limitation, *E. coli*, *Saccharomyces cerevisiae*, or mammalian BHK or CHO cell lines.

The GLP-1 derivatives and analogues of the present invention may be prepared by methods known *per se* in the art. For example, the polypeptide portion may be prepared by chemical synthesis using solid phase protein synthesis techniques, or using recombinant DNA techniques, and the GLP-1 peptide having attached thereto a lipophilic substituent may e.g. be prepared as described in WO 98/08871. Coupling of the group A, comprising the 5- or 6-membered ring system Y, to the N-terminal end of the peptide may similarly be performed using solid phase protein synthesis techniques analogous to the addition of a natural amino acid to the N-terminal end of a peptide, or alternatively, by means of an activated ester. Methods suitable for the addition of unsaturated, partially saturated or saturated heterocyclyl-containing groups, e.g. heteroaryl groups such as imidazole groups, to the N-terminal end of a GLP-1 peptide are further described in EP 0708179-A2.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, *e.g.* as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

For example, injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

According to one procedure, the GLP-1 derivative is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative and a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, *e.g.* hydrochloric acid, or a base, *e.g.* aqueous sodium hydroxide as needed. Finally, the volume of the solution is adjusted with water to give the desired concentration of the ingredients.

A composition for nasal administration of certain peptides may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

The present invention also relates to methods for producing a GLP-1 derivative of the present invention, comprising alkylating, acylating and/or amidating the corresponding GLP-1 analog.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

EXAMPLES

The examples below illustrate the preparation of modified GLP-1 derivatives according to the present invention. In each case, the basic peptide to be modified may, for example, comprise the amino acid residues of GLP-1(8-36), GLP-1(8-37) or GLP-1(8-38). The peptide may of course also contain other modifications as described above.

The following acronyms for commercially available chemicals are used:

DMF : N,N-Dimethylformamide.

DCC : N,N-Dicyclohexylcarbodiimide

NMP : N-Methyl-2-pyrrolidone.

EDPA : N-Ethyl-N,N-diisopropylamine.

TFA : Trifluoroacetic acid.

THF : Tetrahydrofuran.

Pal-ONSu: Hexadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

N^{α}-alkanoyl-Glu(ONSu)-OBu^t: N^{α}-Alkanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

N^{α}-Pal-γ-Glu(ONSu)-OBu^t: N^{α}-Hexadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

N^{α}-Ste-γ-Glu(ONSu)-OBu^t: N^{α}-Octadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester.

Abbreviations:

PDMS: Plasma Desorption Mass Spectrometry

HPLC: High Performance Liquid Chromatography

amu: atomic mass units

EXAMPLE 1

General method A:

Synthesis of alkanoic acid 2,5-dioxopyrrolidin-1-yl ester:

To a solution of the alkanoic acid (34.7 mmol) and N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 mmol) in anhydrous dichloromethane (15 ml), and the resulting reaction mixture was stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised from a mixture of n-heptane and 2-propanol. The precipitate was dried *in vacuo* for 16 h to give the title compound.

Synthesis of Lys(N^{ε}-alkanoyl)-peptide:

To a mixture of the peptide (5.9 μmol), EDPA (21 mg, 164 μmol), NMP (5.8 ml) and water (2.9 ml) was added a solution of the alkanoic acid 2,5-dioxopyrrolidin-1-yl ester (37 μmol), prepared as described above, in NMP (0.5 ml). The reaction mixture was gently shaken for 5 min at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (9.7 mg, 129 μmol) in water (97 μl). The solvent was removed *in vacuo*, and the residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% for 60 minutes.

Coupling of a desired group A comprising the 5- or 6-membered ring system Y to the N-terminal end of the peptide may be performed using solid phase protein synthesis techniques as explained above.

EXAMPLE 2

General method B:

Synthesis of N^{α}-alkanoyl-(L)-glutamic acid α-tert-butyl-γ-(2,5-dioxopyrrolidin-1-yl) diester:

A suspension of the alkanoic acid 2,5-dioxopyrrolidin-1-yl ester (16.2 mmol), prepared as described under General method A, (L)-glutamic acid α-tert-butyl ester (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (50 ml). The resulting solution was washed with 5% aqueous citric acid (2x25 ml). The solvent was concentrated removed *in vacuo* and the residue dissolved in DMF (36 ml). The resulting solution was carefully added to a 10% aqueous solution of citric acid (357 ml) and extracted

with ethyl acetate (200 ml) and dried ($MgSO_4$). The solvent was concentrated removed *in vacuo* to give the crude glutamic diester intermediate. To a mixture of the crude diester, N-hydroxysuccinimide (1.85 g, 16.1 mmol) and anhydrous DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in anhydrous dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent was concentrated removed *in vacuo*. The residue was purified on a silica gel column (40-63 μm) and eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound.

Synthesis of Lys(N^{ε}-(γ-glutamyl(N^{α}-alkanoyl)))peptide

To a mixture of the peptide (4.2 μmol), EDPA (15.3 mg, 119 μmol), NMP (2 ml) and water (1 ml) was added a solution of N^{α}-alkanoyl-(L)-glutamic acid α-tert-butyl-γ-(2,5-dioxopyrrolidin-1-yl) diester (12.7 μmol), prepared as described above, in NMP (135 ml). The reaction mixture was gently shaken for 5 min at room temperature and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (7 mg, 93 μmol) in water (698 μl). A 0.5% aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture was eluted onto a Varian 5g C8 Mega Bond Elut® cartridge, the immobilised compound was washed with 5% aqueous acetonitril (25 ml) and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated *in vacuo*, and the residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column iwa heated to 65°C and the acetonitril gradient is 0-100% for 60 minutes.

Coupling of a desired group A comprising the 5- or 6-membered ring system Y to the N-terminal end of the peptide may be performed using solid phase protein synthesis techniques as explained above.

EXAMPLE 3

Synthesis of N-terminal modified peptides

Peptides were synthesised according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesiser in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols starting with a Fmoc-Gly-Wang resin (NovaBiochem). The protected amino acid derivatives used were commercially obtained Fmoc amino acids, and Adoc-Imidazolylpropionic acid. The derivatives used where side chain protection was needed were: Fmoc-Arg(Pmc), Fmoc-Trp(Boc), Fmoc-Glu(OBut), Fmoc-Lys(Boc), Fmoc-Gln(Trt), Fmoc-Tyr(But), Fmoc-Ser(But), Fmoc-Thr(But), Fmoc-His(Trt) and Fmoc-Asp(OBut), and Adoc-Imidazolylpropionic acid.

The peptides were cleaved from the resin and side chain deprotected in TFA/phenol/thioanisole/water/ethanedithiol (83.25:6.25:4.25:4.25:2.00) for 180 min. The cleavage mixture was filtered and the filtrate was concentrated by a stream of nitrogen. The crude peptide was precipitated from this oil with diethyl ether and washed twice with diethyl ether. After drying the crude peptide was dissolved in 50% aqueous acetic acid and diluted to 10% acetic acid with water and purified by semipreparative HPLC on a 25 mm x 250 mm column packed with 7 μm C-18 silica. The column was eluted with a gradient of acetonitril against 0.05 M $(NH_4)_2SO_4$, pH 2.5 at 10 ml/min. at 40°C. The peptide-containing fractions were collected, diluted with 3 volumes of water and applied to a Sep-Pak® C18 cartridge (Waters part. 51910) which was equilibrated with 0.1% TFA. The peptide was eluted from the Sep-Pak® cartridge with 70% acetonitrile/0.1% TFA, water and isolated from the eluate by lyophilization after dilution with water. The final product obtained was characterised by amino acid analysis, analytical RP-HPLC and by PDMS. Amino acid analysis and mass spectrometry agreed with the expected structure within the experimental error of the method (mass spectrometry +/- 2 amu, amino acid analysis +/- 10%, RP-HPLC showed a peptide purity >95%).

The RP-HPLC analysis was performed using UV detection at 214 nm and a Vydac 218TP54 4.6 mm x 250 mm, 5 μm C-18 silica column which was eluted at 1 ml/min. at 42°C. Two different elution conditions were used: a gradient of 5-60% acetonitrile /0.1 M ammonium sulfate, water pH 2.5; and a gradient of 5-60% acetonitrile, 0.1% TFA / 0.1% TFA, water.

Example 4

Synthesis of desamino-His^7,Arg^{26},Lys^{34} (N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl))) GLP-1 (7-37)-OH.

To a mixture of desamino-His^7,Arg^{26},Lys^{34} GLP-1 (7-37)-OH (14.3 mg, 4.2 μmol), EDPA (15.3 mg, 119 μmol), NMP (2 ml) and water (1 ml) was added a solution of Pal-

Glu(ONSu)-OBu^t (6.84 mg, 12.7 μmol) in NMP (171 μl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (7 mg, 99 μmol) in water (700 μl). A 0.5 % aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture eluted onto a Varian 5g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated *in vacuo*, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (5.6 mg, 35 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3738 +- 3. The resulting molecular weight is thus 3737 +- 3 amu (theoretical value 3737 amu).

Example 5

Synthesis of Cap-Glu(ONSu)-OBu^t.

To a solution of octanoic acid (5 g, 34.7 mmol) and N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 mmol) in anhydrous dichloromethane (15 ml), and the resulting reaction mixture stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised from a mixture of n-heptane (40 ml) and 2-propanol (2 ml). The precipitate was dried in a vacuum drying oven for 16 h to give the intermediate Cap-ONSu. A suspension of the crude ester intermediate (3.9 g, 16.2 mmol), (L)-H-Glu(OH)-OBu^t (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (50 ml). The resulting solution was washed with 5% aqueous citric acid (2x25 ml). The solvent was concentrated *in vacuo* and the residue dissolved in DMF (36 ml). The resulting solution was added drop wise to a 10% aqueous solution of citric acid (357 ml) and extracted with ethyl acetate (200 ml), and dried ($MgSO_4$). The solvent was concentrated *in vacuo* to give the crude glutamic acid intermediate. To a mixture of the crude glutamic acid intermediate, N-hydroxysuccinimide (1.85 g, 16.1 mmol) and DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent concentrated *in vacuo*. The residue was purified on a silica gel column (40-63μ), eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound (0.63 g, 6% over all).

Example 6

Synthesis of desamino-His^7,Arg^{26},Lys^{34} (N$^{\varepsilon}$-(γ-glutamyl(N$^{\alpha}$-octanoyl))) GLP-1 (7-37)-OH.

To a mixture of desamino-His^7,Arg^{26},Lys^{34} GLP-1 (7-37)-OH (14.3 mg, 4.2 μmol), EDPA (15.3 mg, 119 μmol), NMP (2 ml) and water (1 ml) was added a solution of Cap-Glu(ONSu)-OBu^t. (6.8 mg, 12.7 μmol), prepared as described in example 5, in NMP (135 μl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (7 mg, 93 μmol) in water (698 μl). A 0.5 % aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture eluted onto a Varian 5g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated *in vacuo*, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (4.1 mg, 27 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3626 +- 3. The resulting molecular weight is thus 3625 +- 3 amu (theoretical value 3625 amu).

Example 7

Synthesis of Desamino-His^7,Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-glutamyl(N$^{\alpha}$-hexadecanoyl))) GLP-1 (7-37)

To a mixture of desamino-His^7,Arg^{34}-GLP-1 (7-37)-OH (20 mg, 5.9 μmol), EDPA (21.5 mg, 166 μmol), NMP (2.8 ml) and water (1.4 ml) was added a solution Pal-Glu(ONSu)-OBu^t (9.6 mg, 17.8 μmol in NMP (240 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 75 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (9.8 mg, 130 μmol) in water (979 μl). A 0.5% aqueous solution of ammonium acetate (58 ml) was added, and the resulting mixture eluted onto a Varian 5g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated *in vacuo*, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (9.1 mg, 41%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated

molecular ion was found to be 3739 ± 3. The resulting molecular weight is thus 3738 ± 3 AMU (theoretical value 3736 AMU).

Example 8

Synthesis of Myr-GABA-ONSu

To a solution of Myr-ONSu (4 g, 12.3 mmol) in DMF (350 ml) was added EDPA (1.58 g, 12.3 mmol) and γ-aminobutyric acid (1.26 g, 12.3 mmol). The resulting mixture was stirred at ambient temperature for 18 h. Water (50 ml) was added and the solution stirred for 1 h at room temperature. The solvents were removed *in vacuo* to give a solid. The solid residue was dissolved in DMF (75 ml) and the solution added drop by drop to a 5% aqueous solution of citric acid (250 ml). The precipitate collected, washed with water (100 ml) and dried *in vacuo* to give the free acid intermediate (3.65 g, 95%). To a solution of the free acid intermediate (3 g, 9.6 mmol), N-hydroxysuccinimide (1.65 g, 14.4 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.67 g, 19.1 mmol) in DMF (330 ml) was stirred for 18 h at room temperature, and the solvent removed *in vacuo* to give a solid. The solid residue was dissolved in dichloromethane (100 ml) and washed with brine (100 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.8 g, 71%).

Example 9

Synthesis of desamino-His^7,Arg^{34},Lys^{26}(N$^{\varepsilon}$-(γ-aminobutyroyl(N$^{\varepsilon}$-hexadecanoyl))) GLP-1 (7-37)

To a mixture of desamino-His^7,Arg^{34}-GLP-1 (7-37)-OH (20 mg, 8.9 μmol), EDPA (21.5 mg, 166 μmol), NMP (2.8 ml) and water (1.4 ml) was added a solution Pal-GABA-ONSu (7.8 mg, 17.8 μmol) in NMP (181 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (9.3 mg, 125 μmol) in water (93 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (11.6 mg, 55%) was isolated, and the product was

analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3692 ± 3. The resulting molecular weight is thus 3691 ± 3 AMU (theoretical value 3693 AMU).

Example 10

Synthesis of desamino-His^{7},Arg^{34},Lys^{26}(N$^{\varepsilon}$-(β-alanyl(N$^{\gamma}$-hexadecanoyl))) GLP-1 (7-37)

To a mixture of desamino-His^{7},Arg^{34}-GLP-1 (7-37)-OH (25 mg, 7.4 μmol), EDPA (26.8 mg, 208 μmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Pal-β-Ala-ONSu (9.4 mg, 22.2 μmol) in NMP (236 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 130 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 163 μmol) in water (122 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (13.4 mg, 49%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3681 ± 3. The resulting molecular weight is thus 3680 ± 3 AMU (theoretical value 3678 AMU).

Example 11

Synthesis of Ste-GABA-ONSu

To a solution of Ste-ONSu (3 g, 7.9 mmol) in DMF (270 ml) was added EDPA (1 g, 7.9 mmol) and a solution of γ-aminobutyric acid (0.81 g, 7.9 mmol) in water (40 ml). The resulting suspension was stirred at ambient temperature for 18 h, and then concentrated *in vacuo* to a final volume of 50 ml. The resulting suspension was added to a 5% aqueous solution of citric acid (500 ml) whereby a precipitate is formed. The precipitate was collected and washed with water (50 ml), and dried *in vacuo* for 4h to give the free acid intermediate (2.8 g, 97%). To a mixture of the free acid intermediate (2.6 g, 7 mmol), N-hydroxysuccinimide (1.21 g, 10.5 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.69 g, 14 mmol) in NMP (300 ml) was stirred for 70 h, and the solvent removed *in vacuo* to give a solid. The solid residue was dissolved in dichloromethane (100 ml) and washed with brine (2x100 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.2 g, 67%).

Example 12

Synthesis of Arg^{34},Ala^{8}(N^{α}-(imidazol-4-ylprop-2-enoyl),Lys^{26}(N^{ε}-(γ-aminobutyroyl(N^{γ}-hexadecanoyl))) GLP-1 (8-37)

To a mixture of Arg^{34},Ala^{8}(N^{α}-(imidazol-4-ylprop-2-enoyl)-GLP-1 (8-37)-OH (5.6 mg, 1.7 μmol), EDPA (6 mg, 46.2 μmol), NMP (0.78 ml) and water (0.39 ml) was added a solution Pal-GABA-ONSu (2.2 mg, 5 μmol) in NMP (54 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 80 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.7 mg, 36 μmol) in water (27 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (1.9 mg, 31%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3690 ± 3. The resulting molecular weight is thus 3689 ± 3 AMU (theoretical value 3690 AMU).

Example 13

Synthesis of Arg^{34},Ala^{8}(N^{α}-(imidazol-4-ylacetyl),Lys^{26}(N^{ε}-(γ-aminobutyroyl(N^{γ}-hexadecanoyl))) GLP-1 (8-37)

To a mixture of Arg^{34},Ala^{8}(N^{α}-(imidazol-4-ylacetyl)-GLP-1 (8-37)-OH (5.3 mg, 1.6 μmol), EDPA (5.7 mg, 43.9 μmol), NMP (0.74 ml) and water (0.37 ml) was added a solution Pal-GABA-ONSu (2 mg, 4.7 μmol) in NMP (52 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 80 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.6 mg, 34 μmol) in water (26 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (2.2 mg, 38%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3676 ± 3. The resulting molecular weight is thus be 3675 ± 3 AMU (theoretical value 3678 AMU).

Example 14

Synthesis of desamino-His^7,Arg^{34},Lys^{26}(N^{ε}-(γ-aminobutyroyl(N^{γ}-tetradecanoyl))) GLP-1 (7-37)

To a mixture of desamino-His^7,Arg^{34}-GLP-1 (7-37)-OH (25 mg, 7.4 μmol), EDPA (26.9 mg, 208 μmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Myr-GABA-ONSu (9.1 mg, 22.2 μmol), prepared as described in example 8, in NMP (228 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 163 μmol) in water (122 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (10.5 mg, 39%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3667 ± 3. The resulting molecular weight is thus 3664 ± 3 AMU (theoretical value 3662 AMU).

Example 15

Synthesis of desamino-His^7,Arg^{34},Lys^{26}(N^{ε}-(γ-aminobutyroyl(N^{γ}-octadecanoyl))) GLP-1 (7-37)

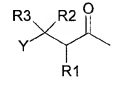
To a mixture of desamino-His^7,Arg^{34}-GLP-1 (7-37)-OH (25 mg, 7.4 μmol), EDPA (26.8 mg, 207 μmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Ste-GABA-ONSu (10.4 mg, 22.2 μmol), prepared as described in example 11, in NMP (259 μl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 170 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 163 μmol) in water (122 μl) and the reaction mixture purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65°C and the acetonitril gradient was 0-100% in 60 minutes. The title compound (7 mg, 25%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3719 ± 3. The resulting molecular weight is thus 3718 ± 3 AMU (theoretical value 3720 AMU).

CLAIMS

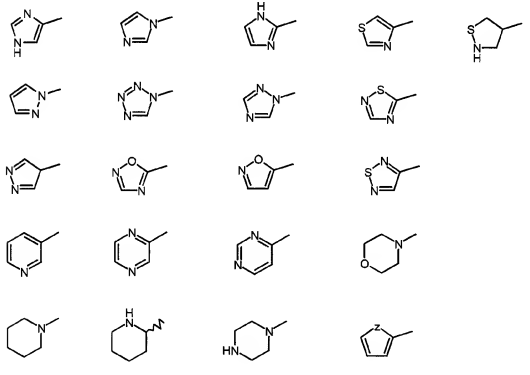
1. A GLP-1 derivative of formula II

A–HN-GLP-1(8-B)-X (II)

wherein

A is:  or  or 

wherein R^1, R^2 and R^3 are independently H, lower alkyl, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy, halogen, SO_2-(lower alkyl) or CF_3, wherein said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl, lower alkoxy, halogen, SO_2-(lower alkyl), NH-CO-(lower alkyl) or CF_3, or R^1 and R^2 may together form a bond; and Y is a five or six membered ring system selected from the group consisting of:



wherein Z is N, O or S, and said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH_2, NO_2, OH, lower alkyl, lower alkoxy, halogen, CF_3 and aryl, provided that A is not histidine;

B is an integer in the range of 35-45; and

X is –OH, $–NH_2$, or a C_{1-6} alkyl amide or C_{1-6} dialkyl amide group;

or an analogue thereof;

wherein a lipophilic substituent (optionally via a spacer) is attached to at least one amino acid residue provided that when the lipophilic substituent is an acyl group and no spacer is present then the acyl group contains at least 12 carbon atoms.

2. The GLP-1 derivative of claim 1, wherein B is 36, 37 or 38.

3. The GLP-1 derivative of claim 1 or 2 which is a derivative of a native form of GLP-1.

4. The GLP-1 derivative of any of claims 1-3, wherein up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue.

5. The GLP-1 derivative of any of claims 1-4, wherein up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code.

6. The GLP-1 derivative of any of claims 1-5, wherein up to six amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code.

7. The GLP-1 derivative of any of claims 1-6, wherein:
B is 36, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{28}, Arg^{34} and Lys^{36};
B is 37, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{25}, Arg^{34}, Lys^{36} and Lys^{37}; or
B is 38, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34}, Lys^{36} and Lys^{38}.

8. The GLP-1 derivative of claim 1 which is of formula III

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  7   8   9  10  11  12  13  14  15  16  17
Xaa-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

 18  19  20  21  22  23  24  25  26  27  28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-
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29 30 31 32 33 34 35 36 37 38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

39 40 41 42 43 44 45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

wherein

Xaa at position 7 is A,
Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 9 is Glu, Asp, or Lys,
Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,
Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,
Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 21 is Glu, Asp, or Lys,
Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,
Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,
Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,
Xaa at position 27 is Glu, Asp, or Lys,
Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,
Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,
Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Met, Leu, Ile, Glu, Asp, or Lys,
Xaa at position 34 is Lys, Arg, Glu, Asp, or His,
Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
Xaa at position 36 is Arg, Lys, Glu, Asp, or His,
Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,
Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C-1-6-ester thereof, (b) amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

wherein

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted,

(ii) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(iii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five or six.

9. The GLP-1 derivative of claim 1 which is a derivative of an analog of GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), or GLP-1(7-39), comprising one or more of the following substitutions:

Ala at position 8 is substituted with Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Glu at position 9 is substituted with Asp or Lys,

Thr at position 11 is substituted with Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,

Ser at position 14 is substituted with Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Val at position 16 is substituted with Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,

Ser at position 17 is substituted with Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Ser at position 18 is substituted with Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Tyr at position 19 is substituted with Tyr, Phe, Trp, Glu, Asp, or Lys,

Leu at position 20 is substituted with Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Glu at position 21 is substituted with Glu, Asp, or Lys,

Gly at position 22 is substituted with Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Gln at position 23 is substituted with Gln, Asn, Arg, Glu, Asp, or Lys,

Ala at position 24 is substituted with Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Ala at position 25 is substituted with Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Lys at position 26 is substituted with Arg, Gln, Glu, Asp, or His,

Glu at position 27 is substituted with Asp or Lys,

Ala at position 30 is substituted with Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Trp at position 31 is substituted with Phe, Tyr, Glu, Asp, or Lys,

Leu at position 32 is substituted with Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Val at position 33 is substituted with Gly, Ala, Ser, Thr, Met, Leu, Ile, Glu, Asp, or Lys,

Lys at position 34 is substituted with Arg, Glu, Asp, or His,

Gly at position 35 is substituted with Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Arg at position 36 is substituted with Lys, Glu, Asp, or His,

Gly at position 37 is substituted with Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Arg at position 38 is substituted with Lys, Glu, Asp, or His, and

Arg at position 39 is substituted with Lys, Glu, Asp, or His, or

(a) a C-1-6-ester thereof, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

wherein

(i) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(ii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five, or six.

10. The GLP-1 derivative of claim 1 which is a derivative of an analog of GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), or GLP-1(7-39), comprising the substitution of Ala at position 8 with Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, wherein the derivative is optionally in the form of (a) a C-1-6-ester thereof, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof, and wherein

(i) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(ii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five, or six.

11. The GLP-1 derivative of claim 10, further comprising the substitution of Lys at position 26 with Arg.

12. The GLP-1 derivative of claim 10 or 11, further comprising the substitution of Lys at position 34 with Arg.

13. The GLP-1 derivative of claim 1 which is a derivative of an analog of GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), or GLP-1(7-39), comprising the substitution of Lys at position 26 with Arg, wherein the derivative is optionally in the form of (a) a C-1-6-ester thereof, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof, and wherein

(i) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(ii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five, or six.

14. The GLP-1 derivative of claim 1 which is a derivative of an analog of GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), or GLP-1(7-39), comprising the substitution of Lys at position 34 with Arg, wherein the derivative is optionally in the form of (a) a C-1-6-ester thereof, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof, and wherein

(i) a lipophilic substituent is attached optionally via a spacer to one or more of (a) the amino group of the N-terminal amino acid, (b) the carboxy group of the C-terminal amino acid, (c) the ε-amino group of Lys, and/or (d) the carboxy group which is part of the R group of Asp or Glu, and

(ii) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one, two, three, four, five, or six.

15. The GLP-1 derivative of claim 14, further comprising the substitution of Lys at position 26 with Arg.

16. The GLP-1 derivative of any of claims 1-15, wherein only one or two Lys are present.

17. The GLP-1 derivative of claim 16, wherein only one Lys is present.

18. The GLP-1 derivative of any of claims 1-17, wherein Lys is at the carboxy-terminus.

19. The GLP-1 derivative of any of claims 1-18, wherein Glu or Asp is adjacent to Lys.

20. The GLP-1 derivative of any of claims 1-19, wherein the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is five.

21. The GLP-1 derivative of any of claims 1-19, wherein the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is four.

22. The GLP-1 derivative of any of claims 1-19, wherein the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is three.

23. The GLP-1 derivative of any of claims 1-19, wherein the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is two.

24. The GLP-1 derivative of any of claims 1-19, wherein the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 is one.

25. The GLP-1 derivative of any of claims 8-24, wherein the amino acids at positions 37-45 are absent.

26. The GLP-1 derivative of any of claims 8-24, wherein the amino acids at positions 38-45 are absent.

27. The GLP-1 derivative of any of claims 8-24, wherein the amino acids at positions 39-45 are absent.

28. The GLP-1 derivative of any of claims 8 and 16-27, wherein Xaa at position 8 is Ala, Gly, Ser, Thr, or Val.

29. The GLP-1 derivative of any of claims 8 and 16-28, wherein Xaa at position 9 is Glu.

30. The GLP-1 derivative of any of claims 8 and 16-29, wherein Xaa at position 11 is Thr.

31. The GLP-1 derivative of any of claims 8 and 16-30, wherein Xaa at position 14 is Ser.

32. The GLP-1 derivative of any of claims 8 and 16-31, wherein Xaa at position 16 is Val.

33. The GLP-1 derivative of any of claims 8 and 16-32, wherein Xaa at position 17 is Ser.

34. The GLP-1 derivative of any of claims 8 and 16-33, wherein Xaa at position 18 is Ser, Lys, Glu, or Asp.

35. The GLP-1 derivative of any of claims 8 and 16-34, wherein Xaa at position 19 is Tyr, Lys, Glu, or Asp.

36. The GLP-1 derivative of any of claims 8 and 16-35, wherein Xaa at position 20 is Leu, Lys, Glu, or Asp.

37. The GLP-1 derivative of any of claims 8 and 16-36, wherein Xaa at position 21 is Glu, Lys, or Asp.

38. The GLP-1 derivative of any of claims 8 and 16-37, wherein Xaa at position 22 is Gly, Glu, Asp, or Lys.

39. The GLP-1 derivative of any of claims 8 and 16-38, wherein Xaa at position 23 is Gln, Glu, Asp, or Lys.

40. The GLP-1 derivative of any of claims 8 and 16-39, wherein Xaa at position 24 is Ala, Glu, Asp, or Lys.

41. The GLP-1 derivative of any of claims 8 and 16-40, wherein Xaa at position 25 is Ala, Glu, Asp, or Lys.

42. The GLP-1 derivative of any of claims 8 and 16-41, wherein Xaa at position 26 is Lys, Glu, Asp, or Arg.

43. The GLP-1 derivative of any of claims 8 and 16-42, wherein Xaa at position 27 is Glu, Asp, or Lys.

44. The GLP-1 derivative of any of claims 8 and 16-43, wherein Xaa at position 30 is Ala, Glu, Asp, or Lys.

45. The GLP-1 derivative of any of claims 8 and 16-44, wherein Xaa at position 31 is Trp, Glu, Asp, or Lys.

46. The GLP-1 derivative of any of claims 8 and 16-45, wherein Xaa at position 32 is Leu, Glu, Asp, or Lys.

47. The GLP-1 derivative of any of claims 8 and 16-46, wherein Xaa at position 33 is Val, Glu, Asp, or Lys.

48. The GLP-1 derivative of any of claims 8 and 16-47, wherein Xaa at position 34 is Lys, Arg, Glu, or Asp.

49. The GLP-1 derivative of any of claims 8 and 16-48, wherein Xaa at position 35 is Gly, Glu, Asp, or Lys.

50. The GLP-1 derivative of any of claims 8 and 16-49, wherein Xaa at position 36 is Arg, Lys, Glu, or Asp.

51. The GLP-1 derivative of any of claims 8 and 16-50, wherein Xaa at position 37 is Gly, Glu, Asp, or Lys.

52. The GLP-1 derivative of any of claims 8 and 16-51, wherein Xaa at position 38 is Arg or Lys.

53. The GLP-1 derivative of claim 8, wherein Xaa at position 26 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

54. The GLP-1 derivative of claim 8, wherein Xaa at position 26 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

55. The GLP-1 derivative of claim 8, wherein Xaa at position 26 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

56. The GLP-1 derivative of claim 8, wherein Xaa at position 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

57. The GLP-1 derivative of claim 8, wherein Xaa at position 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

58. The GLP-1 derivative of claim 8, wherein Xaa at position 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

59. The GLP-1 derivative of claim 8, wherein Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

60. The GLP-1 derivative of claim 8, wherein Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

61. The GLP-1 derivative of claim 8, wherein Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

62. The GLP-1 derivative of claim 8, wherein Xaa at positions 26 and 34 is Arg, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

63. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

64. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

65. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

66. The GLP-1 derivative of claim 8, wherein Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

67. The GLP-1 derivative of claim 8, wherein Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

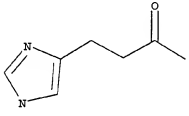
68. The GLP-1 derivative of claim 8, wherein Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

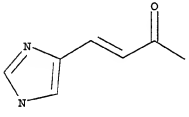
69. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

70. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

71. The GLP-1 derivative of claim 8, wherein Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

72. The GLP-1 derivative of any of the preceding claims, wherein A is selected from the group consisting of:


,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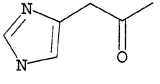
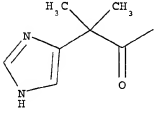
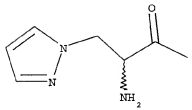

,


, and



73. The GLP-1 derivative of any of claims 1-72 wherein three lipophilic substituents are present.

74. The GLP-1 derivative of any of claims 1-72 wherein two lipophilic substituents are present.

75. The GLP-1 derivative of any of claims 1-72 wherein one lipophilic substituent is present.

76. The GLP-1 derivative of any of claims 1-75, wherein a lipophilic substituent is attached to the amino group of the N-terminal amino acid residue of the parent GLP-1 peptide.

77. The GLP-1 derivative of any of claims 1-76, wherein a lipophilic substituent is attached to the carboxy group of the C-terminal amino acid residue of the parent GLP-1 peptide.

78. The GLP-1 derivative of any of claims 1-77, wherein a lipophilic substituent is attached to the carboxy group which is part of the R group of Asp or Glu of the parent GLP-1 peptide.

79. The GLP-1 derivative of any of claims 1-78, wherein a lipophilic substituent is attached to an ε-amino group of Lys of the parent GLP-1 peptide.

80. The GLP-1 derivative of any of claims 1-79, wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferably from 8 to 25 carbon atoms, most preferably 12 to 24 carbon atoms.

81. The GLP-1 derivative of any of claims 1-80, wherein a lipophilic substituent is attached to an amino acid residue in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with the ε-amino group of Lys of the parent GLP-1 peptide.

82. The GLP-1 derivative of any of claims 1-81, wherein the lipophilic substituent is attached to the parent peptide by means of a spacer.

83. The GLP-1 derivative of claim 82, wherein the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups, which forms an amide bond with an amino group of the parent GLP-1 peptide and an amide bond with an amino group of the lipophilic substituent.

84. The GLP-1 derivative of claim 82, wherein the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys.

85. The GLP-1 derivative of claim 84, wherein the ε-amino group of Lys forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

86. The GLP-1 derivative of any of claims 82-85, wherein the spacer is γ-L-glutamyl, β-L-asparagyl, β-alanyl, glycyl, or α-(γ-aminobutanoyl).

87. The GLP-1 derivative of any of claims 1-86, wherein the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

88. The GLP-1 derivative of any of claims 1-86, wherein the lipophilic substituent is a straight-chain or branched alkyl group.

89. The GLP-1 derivative of any of claims 1-86 wherein the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid, preferably an acyl group of a straight-chain fatty acid.

90. The GLP-1 derivative of claim 89 wherein the acyl group is selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is 10 to 38, preferably $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

91. The GLP-1 derivative of claim 90 wherein the acyl group is tetradecanoyl.

92. The GLP-1 derivative of claim 90 wherein the acyl group is hexadecanoyl.

93. The GLP-1 derivative of any of claims 1-86 wherein the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

94. The GLP-1 derivative of claim 93 wherein the acyl group is selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is from 4 to 38, preferably from 4 to 24, more preferably selected from the group comprising $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

95. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH\text{-}CO(CH_2)_2CO$-, wherein p is an integer of from 8 to 33, preferably from 12 to 28.

96. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

97. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

98. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer of from 8 to 18.

99. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer of from 10 to 16.

100. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NH\text{-}CO(CH_2)_xCH_3$, wherein x is an integer of from 10 to 16.

101. The GLP-1 derivative of any of claims 1-76, wherein the lipophilic substituent with the attached spacer is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NH-CO$(CH_2)_yCH_3$, wherein y is zero or an integer of from 1 to 22.

102. The GLP-1 derivative of any of claims 1-101 which has insulinotropic activity, ability to decrease glucagon, ability to suppress gastric motility, ability to restore glucose competency to beta-cells, and/or ability to suppress appetite/reduce weight.

103. A pharmaceutical composition comprising a GLP-1 derivative of any of claims 1-102 and a pharmaceutically acceptable vehicle or carrier.

104. The pharmaceutical composition of claim 103, further comprising another antidiabetic agent.

105. The pharmaceutical composition of claim 104, wherein the antidiabetic agent is an insulin, more preferably human insulin.

106. The pharmaceutical composition of claim 104, wherein the antidiabetic agent is a hypoglycaemic agent.

107. The pharmaceutical composition of claim 103, further comprising another antiobesity agent.

108. The pharmaceutical composition of claim 107, wherein the antiobesity agent is selected from the group consisting of leptin, amphetamin, dexfenfluramine, sibutramine, orlistat, CART agonists, NPY antagonists, orexin antagonists, H3-antagonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, glucagon, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (Bromocriptin, Doprexin), lipase/amylase inhibitors, PPAR modulators, PXR modulators and TR β agonists.

109. Use of a GLP-1 derivative of any of claims 1-102 for the preparation of a medicament which has a protracted profile of action relative to GLP-1(7-37).

110. Use of a GLP-1 derivative of any of claims 1-102 for the preparation of a medicament with a protracted profile of action for the treatment of non-insulin dependent diabetes mellitus.

111. Use of a GLP-1 derivative of any of claims 1-102 for the preparation of a medicament with a protracted profile of action for the treatment of insulin dependent diabetes mellitus.

112. Use of a GLP-1 derivative of any of claims 1-102 for treating insulin resistance.

113. Use of a GLP-1 derivative of any of claims 1-102 for the preparation of a medicament with a protracted profile of action for the treatment of obesity.

114. A method of treating insulin dependent or non-insulin dependent diabetes mellitus in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of any of claims 1-102 together with a pharmaceutically acceptable carrier.

115. A method of treating obesity in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of any of claims 1-102.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00085

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 14/605, A61K 38/26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, MEDLINE, EMBASE, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 9808871 A1 (NOVO NORDISK A/S), 5 March 1998 (05.03.98)	7-71
P,A		1-6,72-115
	--	
X	EP 0708179 A2 (ELI LILLY AND COMPANY), 24 April 1996 (24.04.96), page 3, line 26 - line 39; page 5, line 48 - page 6, line 22	1-6,72-115
Y		7-71
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 1999	21 -04- 1999
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hampus Rystedt Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00085

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5614492 A (JOEL F. HABENER), 25 March 1997 (25.03.97), column 6, line 47 - column 7, line 62	7-71
A		1-6,72-115
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Y	US 5545618 A (DOUGLAS I. BUCKLEY ET AL), 13 August 1996 (13.08.96), column 2, line 50 - column 4, line 10	7-71
A		1-6,72-115
	--	
A	WO 9629342 A1 (NOVO NORDISK A/S), 26 Sept 1996 (26.09.96)	1-115
	--	
A	WO 9426778 A1 (PROTEIN DELIVERY, INC.), 24 November 1994 (24.11.94)	1-115
	--	
A	WO 9531214 A1 (LONDON HEALTH ASSOCIATION), 23 November 1995 (23.11.95), See esp. page 4, line 24 - line 30	103-105
	--	
A	US 5631224 A (SUAD EFENDIC ET AL), 20 May 1997 (20.05.97), abstract	103,104,106
	--	
A	WO 9731943 A1 (NOVO NORDISK A/S), 4 Sept 1997 (04.09.97), See esp. page 18, line 27 - line 31 and claims 14,15	103,107,108
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00085

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 114,115
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 114 and 115 relate to methods of treatment of the human body, a search has been carried out based on the alleged effects of the claimed compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See next sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00085

The present application relates to a large number of peptide derivatives technically linked together by their homologies to GLP-1 and the presence of a lipophilic substituent and an, optionally substituted, 5 or 6-membered ring structure, e.g. an imidazole, at the N-terminal end of the peptide derivative. The compounds are claimed to have a protracted profile of action. Derivatives of GLP-1 with ring structures attached at the N-terminal, possessing the same effects as the claimed derivatives, are well known in the prior art, e.g. through EP, 708179, A2. The method of introducing lipophilic substituents in order to obtain a protracted profile of action is also known, through WO, 9629342, A1.
No new effect of the claimed GLP-1 derivatives has been shown to arise from a common technical feature of the derivatives, structural or other, which defines a contribution over the prior art. Each new GLP-1 derivative is therefore considered to be a unique invention according to PCT Rule 13.1 and 13.2.

As all GLP-1 derivatives could be searched within one fee, the exact number of inventions has not been calculated.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/DK 99/00085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9808871 A1	05/03/98	AU 3847897 A	19/03/98
		AU 4112497 A	19/03/98
		WO 9808872 A	05/03/98
EP 0708179 A2	24/04/96	AU 3432295 A	02/05/96
		BR 9504452 A	20/05/97
		CA 2160753 A	19/04/96
		CN 1129224 A	21/08/96
		CZ 9502666 A	15/05/96
		FI 954941 A	19/04/96
		HU 73413 A	29/07/96
		HU 9503001 D	00/00/00
		IL 115583 D	00/00/00
		JP 8245696 A	24/09/96
		NO 954055 A	19/04/96
		PL 310961 A	29/04/96
		US 5512549 A	30/04/96
US 5614492 A	25/03/97	US 5118666 A	02/06/92
		AT 110083 T	15/09/94
		DE 3750402 D,T	01/12/94
		EP 0305387 A,B	08/03/89
		SE 0305387 T3	
		EP 0587255 A	16/03/94
		JP 1502746 T	21/09/89
		JP 2583257 B	19/02/97
		US 5120712 A	09/06/92
		WO 8706941 A	19/11/87
US 5545618 A	13/08/96	AT 164852 T	15/04/98
		CA 2073856 A	25/07/91
		DE 69129226 D,T	30/07/98
		DK 512042 T	11/05/98
		EP 0512042 A,B	11/11/92
		SE 0512042 T3	
		ES 2113879 T	16/05/98
		WO 9111457 A	08/08/91
WO 9629342 A1	26/09/96	AU 4939596 A	08/10/96
		BR 9607669 A	16/06/98
		CA 2215739 A	26/09/96
		CN 1181760 A	13/05/98
		CZ 9702877 A	15/04/98
		EP 0815135 A	07/01/98
		NO 974269 A	14/11/97
		PL 322254 A	19/01/98
		US 5869602 A	09/02/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/DK 99/00085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9426778 A1	24/11/94	AU 694919 B	06/08/98
		AU 6946694 A	12/12/94
		CA 2162366 A	24/11/94
		EP 0707596 A	24/04/96
		IL 109619 D	00/00/00
		JP 8510255 T	29/10/96
		US 5359030 A	25/10/94
		US 5438040 A	01/08/95
		US 5681811 A	28/10/97
WO 9531214 A1	23/11/95	AU 2404495 A	05/12/95
		CA 2190112 A	12/05/95
		EP 0762890 A	19/03/97
		GB 9409496 D	00/00/00
		JP 10500114 T	06/01/98
US 5631224 A	20/05/97	AU 3888893 A	21/10/93
		CN 1088835 A	06/07/94
		EP 0631505 A	04/01/95
		JP 7504670 T	25/05/95
		WO 9318786 A	30/09/93
		DK 9300099 U	13/04/93
WO 9731943 A1	04/09/97	AU 1871597 A	16/09/97
		CA 2246733 A	04/09/97
		CZ 9802736 A	16/12/98
		EP 0891378 A	20/01/99
		NO 984005 A	31/08/98